Quarterly Progress Report #9

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Neural Prosthetic Control

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Contents

For this Quarterly Report we concentrated on array development, and more specifically, stability analysis. First there is a summary of the overall objectives of the contract and the tasks, which remain largely the same since the beginning of the project. Sections 3.2-3.5 discuss progress on array implantation, stability testing, and histology

1. **Introduction**

A number of neurological disorders, such as spinal cord injury, MD and ALS result in the inability to make voluntary movements. A major reason for paralysis in these disorders is a disconnection of the signal from a normal brain from the spinal cord or muscles. Devices that can detect and decode motor commands have the potential to restore voluntary actions in these individuals. The purpose of this project is to demonstrate the ability to use neural signals to control real world devices in monkeys; such devices can ultimately serve as prosthetic aids for paralyzed individuals.

Control signals for prosthetic devices can be derived from a number of sources, including the eyes, muscles, and EEG. These signals are, however, rather limited in the number of dimensions they can control. Going beyond a one dimensional control signal is difficult and often interferes with natural behavior. For example, two dimensional EEG control requires full attention to control without distraction (such as gaze shifts). By contrast, populations of neurons appear to contain rich signals, potentially able to control multiple dimensions independently. However, chronic recording of multiple neurons in primates has been technically challenging, the ability to decode neural activity into meaningful control signals is poorly understood and the ability to control devices using such signals is not developed.

The overall goal of this work is to develop a means to bring a robotic arm under near real time neural control using a multineuron signal derived from a recording device that is chronically implanted in a macaque monkey motor cortex. This project has three specific objectives. The **first objective** is to develop and test technologically advanced neural recording devices in a non-human primate model. This work examines the stability, efficiency and biocompatibility of electrode arrays and the suitability of the primary motor cortex as a sight to obtain neural recordings. Once recorded, neural activity must be decoded into meaningful control signals. The optimal methods for such decoding are not obvious. A **second objective** of the project is to examine various decoding methods and evaluate their ability to be useful control signals. This requires mathematical tools and signal processing that reconstructs intended actions from abstract, neurally based motor commands generated in the cortex. This aspect of the project involves fundamental motor control questions, such as what coordinate system is used to encode voluntary actions. **A third objective** of this project is to show that such signals can be used to control devices such as a robotic arm or a computer interface. These devices serve as a proxy for the lost limb and can be used to recreate useful actions like those intended for the arm. Successful completion of these goals would suggest that this approach could be used to restore movement in paralyzed humans.

2. Summary of Related Achievements this quarter

Monkeys are being trained every day on several tasks: radial, tracking, button box in the chair, and also button box at the cage. Performance is continually improving over time. This quarter we implanted a Utah array in MI in monkey (99-2) with the neuroport high density 100 pin low insertion force connector. This connector failed because the metal cap that covers the connector was stuck to it because blood seeped up into the threads and on top of the connector. When the cap was removed, the printed circuit board that sits on top of the connector and has the 100 pads was stuck inside the cap. Consequently, we performed our first array explant, which was very successful. The cortical surface appeared

relatively uncompromised after the array was removed. Array removal was documented with video. We plan to re-implant in the same location next quarter to test the ability for the tissue to be re-implanted. The quality of single cell recordings was analyzed with respect to electrode impedances in two monkeys. In addition, electrode stability analysis was continued.

3.0 Array Development

The goal of the array development of this aspect of the project is to identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex. This requires monkey training in various behavioral tasks, implantation using various modifications in the surgical procedures and in the array assembly and recording to test the quality and stability of units.

3.1 Behavioral training In order to test for motor related neural activity, monkeys are first operantly conditioned to the various arm movement tasks using juice or water reward. Animals are motivated to perform these tasks by restricting access-time to fluids. During training and recording periods, monkeys are allowed as much fluid as they wish to obtain when they perform the training tasks. Fluids are also supplemented after training sessions and on weekends. as approved by the institutional animal care committee. Training tasks are also support the animals' psychological well-being because they provide an additional sources of challenge with positive reinforcement.

3.1.1 Radial direction task: Monkeys are first operantly conditioned (using juice or water reward) to perform an instructed-delay task consisting of visually-guided planar reaching movements from a central holding position to a radially located target. Animals move a two-joint manipulandum in the horizontal plane to direct a cursor from a central hold position to one of eight possible radially positioned targets (6 cm away from start position) viewed on a computer monitor. Hand position is recorded as the x and y location of the manipulandum using a digitizing tablet, with a sampling rate of 200 Hz. The tangential velocity and acceleration of the hand is computed by numerical differentiation using own custom software. A trial is composed of three epochs: a "hold" period during which time the monkey maintains the cursor at the hold position for 0.5 s, a random 1-1.5 s "instructed delay" period during which the target for the forthcoming action appeared but movement is withheld, and a "go" period initiated by target blinking (mean reaction time ~365 ms). Manipulandum position is monitored using a digitizing tablet sampled at 72 Hz.

3.1.2 Continuous tracking task: This task has been developed by our laboratory for a systems analysis approach to describe neural encoding in MI. It overcomes numerous shortcomings of step tracking tasks: correlation of kinematic variables and nonstationarities in behavioral and neural data. This makes it possible to treat each neural spike as an independent sample from a process with a known distribution, a requirement for many statistical tests and for information theoretic analysis. This task uses the same 2 dimensional device as the direction task except that the stimulus must be tracked in a continuous fashion. We generate a broad distribution of movement stimuli that monkeys must track. Data from this task are used to create the linear filters used to test our ability to reconstruct hand motion from neural data.

Our approach is to have the monkey move its hand (the end point effector) across a two dimensional workspace such that the probability distribution of each kinematic variable is as broad as possible (i.e. the monkey will make a series of motions that will, over time, include all possible velocities, positions, etc., within a plane of movement.) For this task monkeys are trained to track a visual target (2 degree white circle on black background) on a computer screen. The target motion is computer controlled to move in a pseudorandom, experimenter determined fashion. The statistics of the motion of the target, and the resultant tracking motion of the monkey's hand, are chosen in such a way that the entropy (the accepted measure of "broadness") of the distribution of motion is maximized under the constraints imposed by reaction time and biomechanical properties of the arm. In other words, the monkey moves its hand so that we sample from the complete space of possible planar arm movements. We hypothesize that it will be possible to mimic the arm kinematics with a prosthetic device (robot arm) by building a series of decoding filters that defines the relationship between the set of kinematic variables and arm movement. Because we have simultaneously recorded neurons, we can use not only the firing rate of each cell, but also the joint or higher order distribution (e.g. covariance) of neuronal activity to extract information about natural, time-varying movement parameters

3.1.3. Button box task. The button task has been developed as a simple version of the radial task (3.1.1) task that can be learned quickly so that monkeys can be made available for testing arrays. Task training is the major rate limiting step to array implantation, since monkeys must be trained before this surgery occurs. This task simply requires the monkey to press one illuminated button arranged in a circle around a central button Buttons are illuminated with a red LED to indicate which button to press for a reward. During training monkeys are shaped to hold to the center button for a 1-4 second random delay, then one peripheral button is illuminated as the target and as a go signal. Successful pressing of the illuminated button is reinforced with liquid. The devices we have developed are introduced in the cage, then monkeys perform the same task in the primate chair, where recordings are performed.

3.2 Array Implantation*:* Arrays are implanted in the MI arm representation, medial to the spur of the arcuate sulcus, abutting the central sulcus. The ability to locate arm related neurons using these sulcal landmarks has been 100% successful in our tests. The UEA microelectrode arrays consist of 100, 1.0mm long platinized tip, silicon probes arranged in a square grid on 400μm centers. Impedances between 50-500 kΩ (1 nA, 1kHz sine wave) (Nordhausen et al., 1996). Arrays are wired to connectors contained in a custom designed titanium percutaneous pedestal with using 1 mil gold, Teflon insulated wire (the assembly is custom fabricated for us by Bionics (BTI)). Two extra wires (50.8 μm diameter, Pt-Ir 20%) with approximately 5.0 mm of the terminal insulation removed are inserted subdurally and used as reference and as backup. The bundle of gold wires is coated with silicone elastomer (MDX4-4210, Dow Corning, MI). The back of the array and percutaneous connectors are coated with silicone elastomer to mechanically protect the wires and maintain electrical insulation at the bond pad sites.

The array is inserted rapidly into the cortex using a calibrated, pneumatically propelled mass, and typically, the array is and cortical surface is covered by a Teflon sheet. The dura is then loosely closed and this area is covered by a sheet of Gortex followed by silicon elastomer. Finally the entire region is covered with cranioplast cement which is anchored to the skull through a series of titanium bone screws.

Array implantation procedures initially involved several foreign bodies, which are undesirable if arrays are to be implanted in humans, and have been the source of infection (between the acrylic and the bone) in cases, especially with long survival times of years. Foreign bodies in our earliest version of the implant procedure include placement of Teflon sheets above and below the dura, addition of silicone elastomere and most significantly the use of acrylic sealant. We have largely replaced the acrylic seal with a titanium mesh (Timesh) covering in 5 monkeys. Successful animal recovery has been achieved in every case and there is no evidence that this procedure affects recording quality or stability. We have continued to use Timesh to isolate the dura from the arachnoid membrane.

During the past quarter we implanted one Neuroport (Bionics, LLC) array in monkey 99-2. Monkey 99-2 was implanted with the new 100 channel compact connector, but the array had to be removed due to a broken connector. The metal cap that covered the connector was stuck to it because blood seeped up into the threads and on top of the connector. When the cap was removed, the printed circuit board that sits on top of the connector and has the 100 pads, was stuck inside the cap due to the blood. The plan in the next quarter is to re-implant on the same side. This was the first array explant, and the tissue under the array showed no gross damage, although some dural and pial discoloration was noted. We plan to implant another array in the same location.

Implantation surgeries have proceeded with some challenges. Two difficulties encountered have been (1) positioning of the array during surgery because the wire bundle is stiff and non compliant and (2) positioning of the reference wires, which are springy. We have been discussing the need for a more flexible cabling system between the array and its connector with BTL, but it appears that this will require significant development time. For the reference wire, BTL has fabricated new arrays with larger diameter (100 μm+) reference wires. These have helped ease the positioning difficulties of the reference wires, but this remains problematic to handle. We expect to have an improved 100 channel compact connector ready for implantation in January 2002.

3.4 Array Testing

Recording Stability: The ability to maintain the same cells each day of recording by the UIEA is not known and is important in the design of a prosthetic device. Decoding algorithms must be able to deal with instabilities. To measure stability similarity measures including the autocorrelation function (to determine firing pattern), movement related activity, directional tuning properties, and spike waveform.

Data obtained by Dr. Nakata demonstrated that neural recordings could be obtained 850 days after array implantation in one monkey. The number of cells that were present varied from day to day from a few cells to over 30 cells in the three monkeys studied so far. The yield from each array also varied from day to day. Cells were recorded from 10% to over 70% of the available electrodes on an array with a mean of 40%. Individual electrode impedances ranged from 0 to 300 K ohm for one array, 100 to 800 for the other two arrays

evaluated with the majority of electrodes having impedances of 100-400 K Ohms respectively. Our analysis showed that the quality of the recording was not significantly correlated with electrode impedance , but there was a trend toward better quality at impedances in the 100-200 K ohm range as opposed to those with higher or lower impedances.
During this quarter in depth analysis of data from one monkey was begun (99-3) to evaluate the day to day variability in the units recorded and the number of electrodes with viable cell recording. Variables being investigated include

1- Firing pattern of cells such as preferred direction and histograms centered on start of movement
2- Autocorrelation function of the cells
3- Shape of the cells including amplitude, duration and direction of force
4- Yield of cells on a given array

These variables will also be evaluated in four additional monkeys with long term recordings.

Data analyzed from 99-3 to date reveals that the number of cells recorded could shift abruptly across one day (eg., 28 to 23 cells). The channels with cells on them were the same with a general decrease in signal to noise at many sites. 12 out of the 28 cells had lower quality recordings and 16 of the 28 cells remained constant. The cells were distributed throughout the array, so that the change could not be attributed to recording from one location. Nevertheless accurate decoding of hand position based on units recorded with these recordings was possible.

Head stabilization: Lack of head stabilization has created a number of difficulties in recording. Movement of some versions of the array connectors (most notably the Miraco ribbon cable connectors to the preamplifiers) produce significant electrical artifact. Some monkeys rotate in the primate chair, which results in damage to the cabling. Consequently, we developed and implemented a head restraint system. This has introduced some delays in implantation and testing because we needed to design and manufacture head posts and then implant each monkey. Head post surgery requires at least a six week period to allow integration of the posts into the skull. In addition, the initial version of the headposts had small bases that were not sufficiently stable, so we designed and had manufactured a stronger, one piece post/base units, with 2 screws per foot (total of 6 screws). During this quarter we implanted four additional monkeys with head bolts for head stabilization during recording in preparation for array implantation.

3.5 Histological analyses*:* **The goal of histological analysis is to determine tissue reaction to the UIEA. We test for cell loss and reaction using both thionin cell stain and GFAP, to test for glial reactivity. During this quarter we began an examination of tissue from B023, B147, 115-97, and 99-7. No monkeys with arrays were perfused this quarter.**